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5-$HT_{2A/C}$ receptors mediate the antipsychotic-like effects of alstonine

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ABSTRACT

The purpose of this study was to determine the effects of alstonine, an indole alkaloid with putative antipsychotic effects, on working memory by using the step-down inhibitory avoidance paradigm and MK801-induced working memory deficits in mice. Additionally, the role of serotonin 5-$HT_{2A/C}$ receptors in the effects of alstonine on mouse models associated with positive (MK801-induced hyperlocomotion), negative (MK801-induced social interaction deficit), and cognitive (MK801-induced working memory deficit) schizophrenia symptoms was examined. Treatment with alstonine was able to prevent MK801-induced working memory deficit, indicating its potential benefit for cognitive deficits now seen as a core symptom in the disease. Corroborating previously reported data, alstonine was also effective in counteracting MK801-induced hyperlocomotion and social interaction deficit. Ritanserin, a 5-$HT_{2A/C}$ receptor antagonist, prevented alstonine's effects on these three behavioral parameters. This study presents additional evidence that 5-$HT_{2A/C}$ receptors are central to the antipsychotic-like effects of alstonine, consistently seen in mouse models relevant to the three dimensions of schizophrenia symptoms.

1. Introduction

Although schizophrenia was first described as dementia (*praecox dementia*), cognitive deficits are increasingly regarded as the core symptom of the disease and, unfortunately, the one where treatment failure is more evident (Insel, 2010). More specifically, problems with working memory (WM) are seen to be one aspect of cognitive processes that have a substantial and broad impact on the daily activities of schizophrenic patients (Silver et al., 2003).

Almost 60 years after the introduction of the first antipsychotic in pharmacotherapy, clinical trials still clearly show that improved treatments for psychosis are sorely needed (Insel, 2010). Moreover, the superiority of the second-generation antipsychotics (SGA) is now under question (Anil Yağcioğlu, 2007; Hamann et al., 2003). The modest and controversial effects of antipsychotics on cognitive deficits and negative symptoms, combined with the associated unwanted side effects, result in discontinued treatments (Lieberman et al., 2005) reinforcing the need for drugs with a better profile. Overall, the clinical data suggest that significant improvement in the treatment of schizophrenia is likely to require drugs with an innovative mechanism of action (Gründer et al., 2009).

We have reported the antipsychotic-like effects of alstonine, a putative antipsychotic, which consistently differ from the effects of known drugs in various mouse models (de Moura Linck et al., 2008; Elisabetsky and Costa-Campos, 2006; Linck et al., 2011). Alstonine is an indole alkaloid present in plant species traditionally used in Nigeria to treat mental illnesses, and its mechanism of action remains unclear (Costa-Campos et al., 1998). Importantly, D_2 blockade does not appear to play an important role in alstonine's antipsychotic-like effects, whereas its anxiolytic effects depend on serotonin 5-$HT_{2A/C}$ receptor (Costa-Campos et al., 2004). Alstonine-induced increases in serotonin (5-HT) and 5-hydroxyindole acetic acid (5-HIAA) in mouse frontal cortex and striatum further suggest its modulatory effect on this neurotransmitter system (Linck et al., 2011).

The validity of the glutamatergic hypothesis of schizophrenia was notably reinforced by the observation that NMDA antagonists (such as phencyclidine and ketamine) induce schizophrenia-like symptoms in normal volunteers and worsen symptoms in schizophrenic patients (Javitt, 2010). Accordingly, animal models based on NMDA receptor antagonists have been given preference over the older dopamine based rodent models, especially because the latter display the full array (negative, positive and cognitive) of symptoms observed in schizophrenia (Large, 2007).

The first purpose of this study was to evaluate the effects of alstonine on MK801-induced working memory deficit in mice. Additionally, we further examined the role of 5-$HT_{2A/C}$ receptors in alstonine's effects on mouse models associated with positive, negative and cognitive schizophrenia symptoms.

Abbreviations: 5-HIAA, 5-hydroxyindole acetic acid; DOPAC, dihydroxyphenylacetic acid; HVA, homovanillic acid; 5-HT, serotonin.

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2. Methods

2.1. Animals

Experiments were performed with male (CF1) adult albino mice (40–45 g) obtained from Fundação Estadual de Produção e Pesquisa em Saúde (FEPPS) at 2 months of age. Mice were maintained in our own animal facility under controlled environmental conditions (22 ± 1 °C, 12-h light/dark cycle, free access to food [Nuvilab CR1] and water), for at least two weeks before the experiments.

The study was approved by the University ethics committee (approval #18236); all procedures were carried out in accordance with institutional policies on experimental animal handling.

2.2. Drugs

Clozapine and sulpiride were purchased from Sigma Chemical Co. (St. Louis, MO, USA); MK801 (dizocilpine) and ritanserin were from Research Biochemicals International (Natick, MA, USA). Clozapine and sulpiride were solubilized in HCl (1 N), and the pH adjusted to 6.0 with NaOH 1 N; ritanserin was dissolved in 10% dimethyl sulfoxide (DMSO); all other drugs were diluted in distilled water. Pilot studies showed that DMSO 10% did not affect any of the behavioral tests (data not shown); hence, saline was used as a blank control. Treatments were administered intraperitoneally (0.1 mL/10 g of body weight). With the same dose and timing alstonine does not alter locomotion or social interaction (Costa-Campos et al., 2004; de Moura Linck et al., 2008).

2.3. Isolation and identification of alstonine

Alstonine hydrochloride used in this study was isolated from the fruit rinds of *P. nitida* Stampf Th. et H.Dur. (Apocynaceae). The separations used pH-zone-refining counter-current chromatography as previously detailed (Okunji et al., 2005, 2011). Briefly, the experiment was performed with a two-phase solvent system composed of methyl tert-butyl ether (MtBE)–acetonitrile–water (2:2:3, v/v), where triethylamine (TEA) was added to the upper organic stationary phase as a retainer, and hydrochloric acid (HCl) to the aqueous mobile phase as an eluter. The sample solution was prepared by dissolving 15.0 g of alkaloid fraction of the methylene chloride extract of *P. nitida* in 100 mL of a phase mixture consisting of equal volumes of each phase. The separation was initiated by completely filling the column with the stationary phase (LC pump) before loading the sample; the mobile phase was pumped into the column at 2 mL/min while the column was rotated at 834 rev/min in the combined head to tail elution mode (Shinomiya et al., 1993). The absorbance of the eluate was continuously monitored at 280 nm and 4 mL fractions were collected. The pH of each eluted fraction was measured with a pH meter and fractions were dried using a Speed Vac. Identification of pH-zone refining counter-current chromatography pure fractions was carried out by using thermospray liquid chromatography-mass spectrometry (LC-MS) and by TLC co-elution experiments with reference alstonine samples provided by InterCEDD, Nsukka, Nigeria. The purity of the isolated alstonine sample was 98%.

2.4. Does alstonine improve working memory deficit?

Step-down inhibitory avoidance: The protocol was adapted from Barros et al. (2005). Mice were habituated to the dimly lit experimentation room for at least 30 min before the procedure. The inhibitory avoidance training apparatus was a plastic box of 30 × 30 × 40 cm, with a fixed platform (5 × 5 × 4 cm) at the center of the grid floor. Mice were individually placed on the platform, and the latency to step-down (four paws on the grid) was automatically recorded in training and test sessions. In the training session, upon stepping down, the mouse received a 0.3 mA scrambled foot shock for 5 s. Test sessions were performed 10 s later, with the same procedure except that no shock was administered after stepping down; a 300-s cut-off time was set for stepping down.

2.4.1. Working memory assessment

Mice (n = 14–17) were treated with saline, clozapine (2 mg/kg), sulpiride (10 mg/kg) or alstonine (0.5 or 1 mg/kg). Thirty minutes after treatment mice were subjected to the training session.

2.4.2. MK801-induced working memory deficit

Mice (n = 23–31) were likewise treated with saline, clozapine, sulpiride or alstonine; 30 min later mice received a second treatment with either saline or MK801 (0.05 mg/kg). The step-down training session was performed 30 min after the last treatment.

2.5. Are the effects of alstonine dependent on 5-$HT_{2A/C}$ receptors?

In order to evaluate the involvement of 5-$HT_{2A/C}$ on alstonine antipsychotic-like effects mice were pre-treated with the 5-$HT_{2A/C}$ receptor antagonist ritanserin before behavioral tests. Drug doses and administration schedules were based on Su et al. (2007), as well as on pilot studies showing that ritanserin was devoid of effects *per se*.

2.5.1. MK801-induced working memory deficit

After habituation mice (n = 9–17) received saline or the 5-$HT_{2A/C}$ antagonist ritanserin (0.1 mg/kg); 10 min later animals were treated with saline or alstonine 1 mg/kg, followed 30 min later by a third administration of either saline or MK801 (0.05 mg/kg). Working memory was tested as described above, 30 min after the last treatment.

2.5.2. MK801-induced social withdrawal

Method was adapted from Rung et al. (2005). Mice were acclimatized to a reversed 12-h light cycle (lights on at 20:00 h), housed at 8/cage (familiar group) for 2 weeks before the experiments. Mice were randomly assigned to groups (n = 8–13 pairs) that received saline or ritanserin (0.1 mg/kg), and 10 min later were treated with saline or alstonine 1 mg/kg. Social withdrawal was induced with MK801 (0.3 mg/kg), given 30 min after the second saline or ritanserin treatment (Rung et al., 2005). Experiments were performed 30 min after the last treatment, in a faintly lit room (red bulb, 40 W); the social interaction apparatus (test box) consisted of a topless transparent acrylic box (25 × 20 × 20 cm). Forty-eight and 24 h before the test mice were individually submitted to 10 min habituation sessions in the test box. Then, on the test day, mice were allocated to selected pairs so that the two animals came from unfamiliar groups (different home cages), had matching body weights, and received the same drug treatment. The behavior of each pair was video-recorded in the test box for 10 min; the time spent in social interaction (sniffing and grooming the partner, following, mounting, and crawling under or over the partner) was later analyzed by a trained observer, blind to experimental groups, using the software The Observer® XT5.0 (Noldus Information Technology, Wageningen, The Netherlands). Passive contact (sitting or lying with bodies in contact) was not considered as social interaction.

2.5.3. MK801-induced hyperlocomotion

The method was adapted from Ninan and Kulkarni (1998). Activity cages (45 × 25 × 20 cm, Albarsch Electronic Equipment, Porto Alegre, Brazil) were equipped with three parallel photocells, which automatically recorded the number of crossings. Mice (n = 6–9) were treated with saline or ritanserin (0.1 mg/kg), and 10 min later with saline or alstonine 1 mg/kg; 30 min after the second treatment the animals received saline or MK801 (0.25 mg/kg). Mice were individually placed in the activity cages 30 min after the last administration, and locomotion was recorded from the 5th minute for 10 min (first 5 min considered as exploratory behavior).

2.6. Statistics

Step-down inhibitory avoidance results are expressed as median ± interquartile ranges; other data are presented as mean ± standard error of the mean (SEM). Data were analyzed with SPSS for Windows, version 17. The results from step-down avoidance failed to satisfy the assumptions for normality and homogeneity of variance; therefore, nonparametric analyses were applied. Wilcoxon's test was used to compare training and test latencies within groups, while Kruskal–Wallis/Mann–Whitney U was used to compared the latencies among the groups. All other data did satisfy the assumptions of normality and homogeneity of variance, and were analyzed by one-way analysis of variance (ANOVA). The analysis focused on the effects of ritanserin on MK801-induced social withdrawal and hyperlocomotion where the effects of alstonine in these models were previously established. SNK post-hoc test was used where appropriate to analyze differences between the groups. Statistical significance was set at $p<0.05$.

3. Results

Neither alstonine, nor ritanserin, clozapine, sulpiride or MK801 0.05 mg/kg significantly altered locomotion at the doses used in the study (data not shown).

3.1. Does alstonine improve working memory deficit?

As previously reported (Barros et al., 2005), with the adopted training paradigm consistently longer test latencies were observed in all groups, confirming that working memory can be reliably assessed using this procedure. As can be seen in Fig. 1A, neither alstonine, clozapine nor sulpiride modified working memory (comparable training [$H_{(4)}=3.13$] and test session [$H_{(4)}=1.76$]), with test session latencies significantly longer than training ones ($p<0.05$ Wilcoxon).

MK801 effectively induced working memory deficit (Fig. 1B). Mann–Whitney showed reduced test latencies in the saline group treated with MK801 in comparison with controls ($H_{(5)}=19.2$, $p=0.018$); accordingly, in this group no significant differences exist between training and test session latencies (Wilcoxon, $p=0.76$). Clozapine, sulpiride and alstonine effectively prevented the MK801-induced working memory deficit ($p<0.01$, Wilcoxon for test × training session latencies in all treatment groups).

3.2. Are the effects of alstonine dependent on 5-$HT_{2A/C}$ receptors?

3.2.1. Working memory deficit

The alstonine preventive effect against MK801-induced working memory deficit (Wilcoxon, $p=0.001$) was abolished by pretreatment with ritanserin (Wilcoxon, $p=0.13$). Training session latencies were comparable [$H_{(5)}=4.18$] (Fig. 2A).

3.2.2. Social withdrawal

One-way ANOVA revealed a significant difference between groups ($F_{5,96}=8.68$) (Fig. 2B). SNK indicated that MK801 clearly reduced social interaction time ($p<0.01$) in relation to control. SNK showed that pretreatment with ritanserin modified the effects of alstonine (but not MK801 *per se*) on social interaction ($p<0.05$); while alstonine prevented the effect of MK801 on social interaction ($p<0.05$), this effect is abolished by pre-administration of ritanserin ($p>0.05$).

3.2.3. Hyperlocomotion

As shown in Fig. 2C, there was a significant effect of treatments in locomotor activity ($F_{5,54}=9.83$). SNK revealed that, as expected, MK801 significantly ($p<0.01$) increased crossings in relation to control. Although alstonine prevented the MK801-induced hyperlocomotion ($p<0.05$), pre-treatment with ritanserin abolished this effect ($p>0.05$).

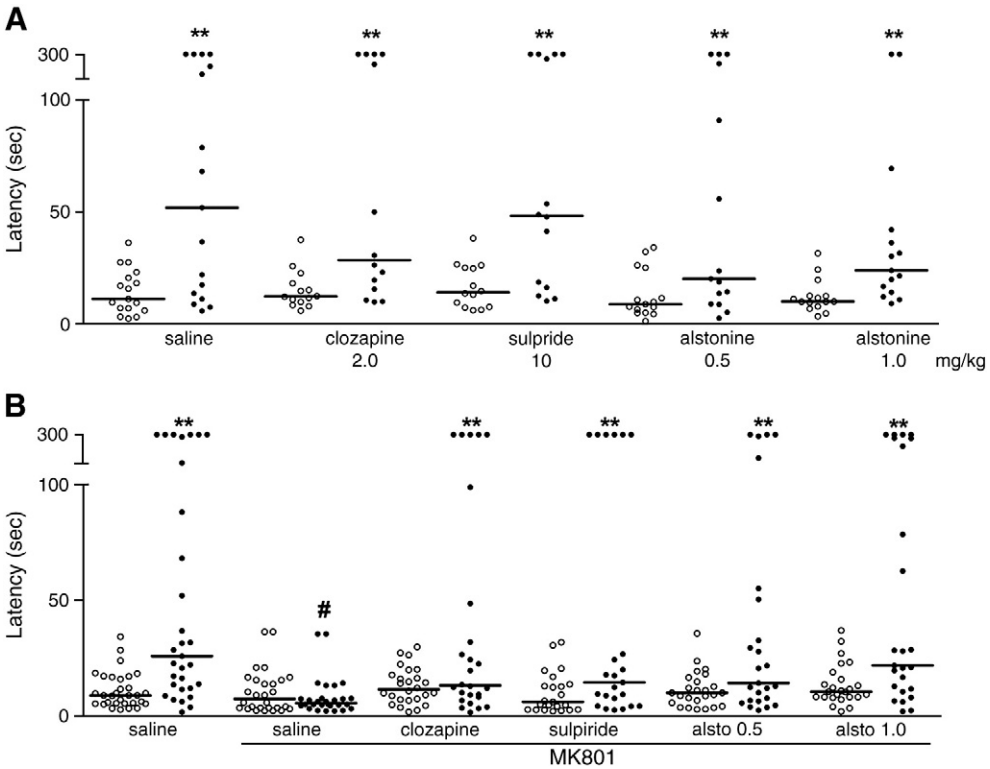

Fig. 1. Alstonine effects on inhibitory avoidance working memory (n = 14–17) (A) and MK801-induced deficit (n = 23–31) (B). Open dots (○) represent training latencies and closed dots (●) test latencies. Lines represent median. ** = $p<0.01$ test × training (Wilcoxon). # = $p<0.01$ compared to saline test session latency (Kruskal Wallis/Mann–Whitney).

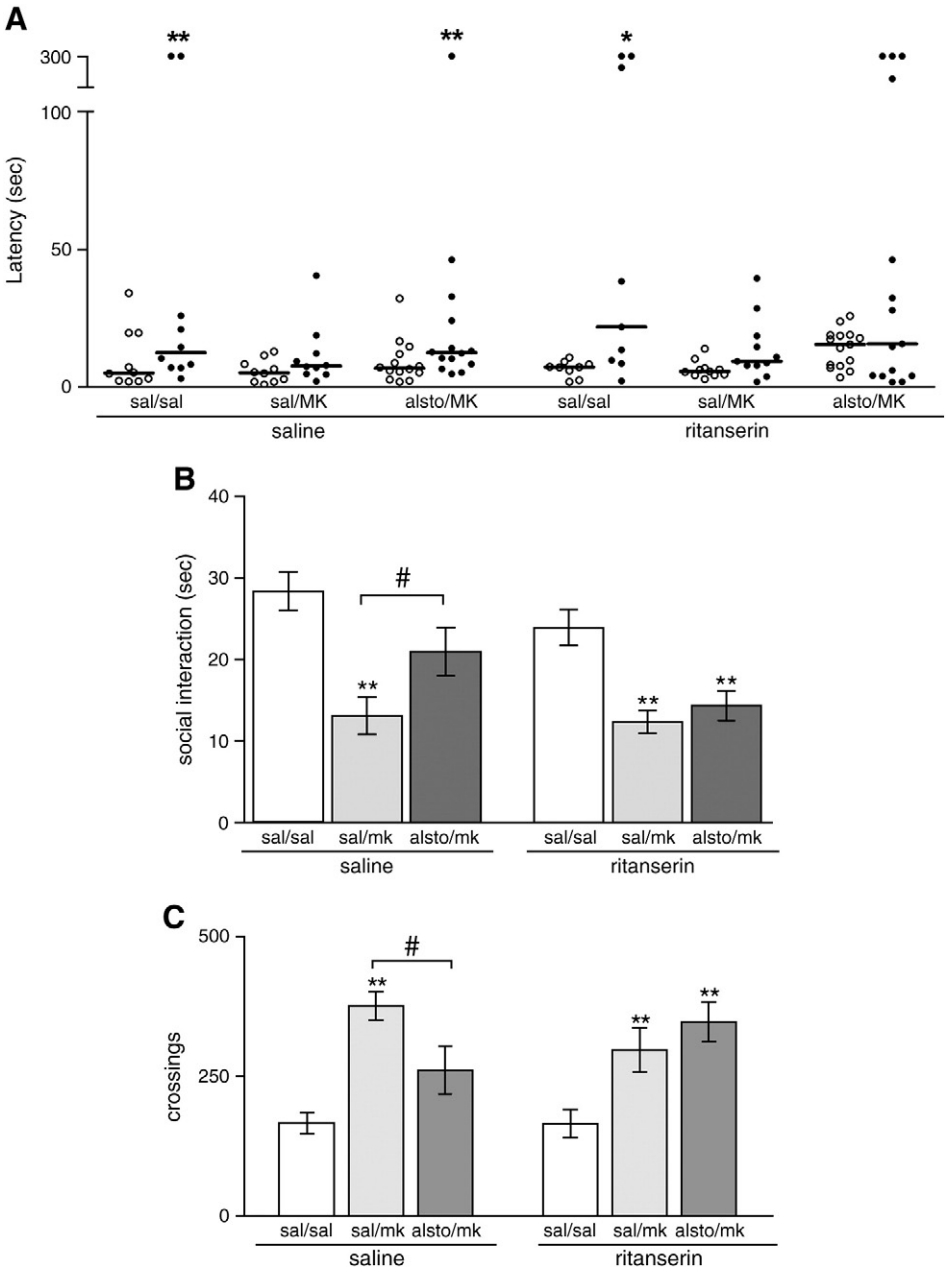

Fig. 2. Ritanserin modifies alstonine effects on working memory deficit (n = 9–17) (A), social withdrawal (n = 8–13 pairs) (B), and hyperlocomotion (n = 6–8) (C). 2A open dots (○) represent training latencies and closed dots (●) test latencies (sec). Lines represent median (sec). * = $p<0.05$, ** = $p<0.01$ test × training (Wilcoxon). 2B columns represent time spent on social interaction (sec, mean ± S.E.M). 2 C columns represent crossings (mean ± S.E.M); ** = $p<0.01$ compared with control, and # = $p<0.05$ compared to sal/sal/MK.

4. Discussion

Though effective treatments are not available (Harvey, 2009; Keefe et al., 2007), several authors advocate a more careful clinical assessment of cognitive deficits in schizophrenics (Keefe et al., 2007; Keefe and Fenton, 2007; Wykes et al., 2007), since the former are currently considered a key component of schizophrenia (Barch, 2005). Special attention has been given to working memory deficits, directly associated with troublesome daily tasks, communication, social relations, and executive activities (Hyman and Fenton, 2003; Silver et al., 2003).

In order to assess working memory we used the inhibitory avoidance paradigm with a 10 s training-test interval (Bianchin et al., 1999). Results show consistently longer test sessions indicating that memory is reliably evaluated, and also that a significant deficit (amnesia) is induced by MK801 with this protocol. Treatment with alstonine was effective in preventing the MK801-induced deficit. It is noteworthy that animal models based on NMDA antagonists such as MK801 are regarded as having reasonable face validity and predictive value (Large, 2007; Rujescu et al., 2006).

We further show that pre-treatment with ritanserin reliably blocked the effects of alstonine on these mouse models of cognitive deficit (MK801-induced working memory deficit), positive (MK801-induced hyperlocomotion) and negative (MK801-induced social withdrawal) schizophrenia symptoms. This body of results is consistent with the hypothesis that 5-$HT_{2A/C}$ receptors are involved in alstonine's antipsychotic-like profile, and consistent with its effects on mouse models of anxiety (Costa-Campos et al., 2004). Indeed, atypical antipsychotics act as 5-$HT_{2A/C}$ receptor antagonists and/or inverse agonists (Meltzer and Massey, 2011), and this serotonergic modulation is thought to be crucial for the purported advantages of these

medications over classical agents (Gründer et al., 2009). Additional evidence for the role of serotonin in alstonine's mechanism of action is that serotonin and 5-HIAA levels were found to be increased in mouse frontal cortex and striatum after alstonine administration (Linck et al., 2011).

Even though the neuropathological basis of schizophrenia remains to be elucidated, accumulating evidence indicates that hypofunction of NMDA receptors does occur in this disease (Belforte et al., 2010; Kristiansen et al., 2007; Paz et al., 2008). It is to be expected that altered NMDA function would imply meaningful changes in various neurotransmission systems (including GABA, 5-HT, DA) contributing to the complex patterns of behavioral alterations seen in schizophrenic patients (Kristiansen et al., 2007). It is relevant to this discussion that NMDA blockade has been shown to lead to a 5-HT_{2A}-dependent increase in serotonergic transmission (López-Gil et al., 2007; Martin et al., 1998). Similar modulation is illustrated by the finding that the increased firing rate in prefrontal cortex glutamatergic neurons induced by MK801 (0.05 mg/kg, i.p., as in this study) can be prevented by ritanserin (Labonte et al., 2009).

In 2009, natural product-derived drugs represented 50% of all approved new drugs; moreover, between 2005 and 2007, of the 13 natural products-derived drugs approved in the USA 5 were the first member of a new class (Li and Vederas, 2009). While this clearly shows the role of natural products in pharmaceutical innovation, it is arguable that natural compounds identified through ethnopharmacological analysis of traditional uses may be especially useful in the case of illnesses with an ill-defined pathophysiology (Patwardhan, 2005), such as schizophrenia (Elisabetsky, 2007). Considering the pitfalls of currently available medication, the coherence of the animal data presented here with claims of therapeutic benefit in mentally ill patients is promising. A clear characterization of alstonine's mechanism of action is therefore warranted and necessary, including *in vitro* functional binding to clarify the exact nature of the interaction between alstonine and serotonin receptor subtypes.

5. Conclusion

Alstonine is an indole alkaloid with an antipsychotic-like profile in mouse models; it has been identified as the main component in plant-based formulations used to treat mentally ill patients in Africa. We here show that alstonine prevents MK801-induced working memory deficit in mice. Additionally, ritanserin blocked the effects of alstonine on mouse models of cognitive deficit, positive and negative symptoms in schizophrenia. In agreement with current understanding of the pharmacodynamic basis of atypical antipsychotic action, 5-$HT_{2A/C}$ receptors are implicated in alstonine's effects.

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